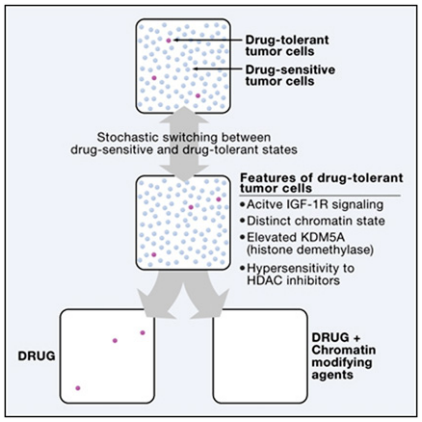
In This Issue

Cell



Reversing Drug Resistance

PAGE 69

Cancer drug efficacy is severely limited by the development of drug resistance. By modeling acquired drug resistance in various human cancer cell lines, Sharma et al. identify a subpopulation of cells that transiently exhibit a ''drug-tolerant'' phenotype associated with a distinct chromatin state that requires particular chromatin-modifying enzymes. Thus, disrupting drug tolerance via agents that affect chromatin dynamics may yield a therapeutic opportunity to prevent the development of drug resistance.

Telomeres, Tetraploidy, and Tumorigenesis

PAGE 81

The formation of tetraploid cells is thought to be an early step in the generation of aneuploid human cancers. In this issue, Davoli et al. report that tetraploidization can be induced by telomere dysfunction. They show that the persistent DNA damage signal elicited by dysfunctional telomeres leads to bypass of mitosis and entry into a second S phase in cells that lack p53. Telomere attrition is common in human cancer, and thus this tetraploidization mechanism presents a likely route to tumor aneuploidy in humans.

Avoiding Entanglements in Meiosis

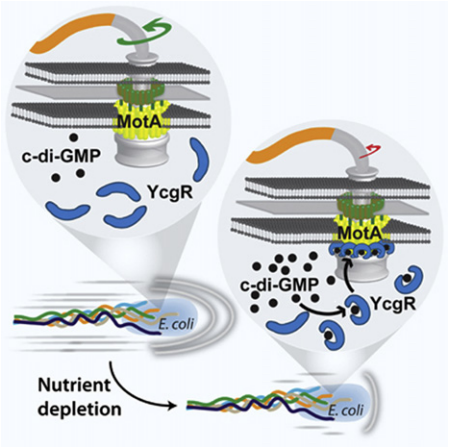
PAGE 94

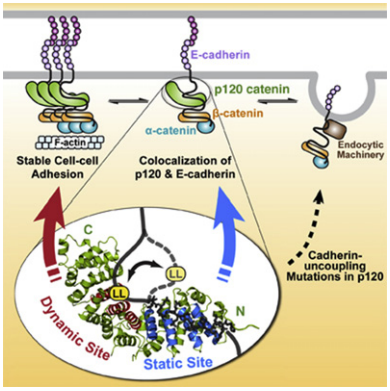
Chromosome pairing is a central issue for meiosis: it involves not only recognition of homology but also juxtaposition of entire chromosomes. Storlazzi et al. now show that three recombination proteins play direct roles in pairing before their known effects on recombination. In addition, these factors also play defined roles in avoiding entanglement of paired homologs. Together, these results provide the first molecular insights into meiotic pairing and interlock resolution.

Bacteria Announce Braking News

PAGE 107

Bacteria swim by means of rotating flagella. Motile bacteria can follow chemical gradients and control the direction of their movement with the help of sensory machinery. Here Boehm et al. show that bacteria can also adjust their swimming velocity in response to changing environmental conditions, like the depletion of nutrients. Swimming velocity is controlled by the synergistic action of at least five signaling proteins that adjust the cellular concentration of cyclic di-GMP.





Cat Got Your Juxtamembrane Domain?

PAGE 117

p120 catenin (p120) helps retain adhesion complexes at the cell surface by binding directly to cadherin's cytoplasmic juxtamembrane domain (JMD). Ishiyama et al. combine structural and functional approaches to reveal that p120 stabilizes E-cadherin by protecting an endocytic motif within the JMD through two distinct interfaces. These results provide insights into the significance of p120-regulated stability of cadherin-catenin complexes in both adherens junction formation and neuronal synapse development.

Setting a New PAR for RNP Binding Site Identification

PAGE 129

RNA transcripts are subject to posttranscriptional gene regulation involving hundreds of RNA-binding proteins (RBPs) and microRNA-containing ribonucleoproteins (miRNPs). In this issue, Hafner et al. report PAR-CLIP, a method to determine transcriptome-wide binding sites of RBPs and miRNPs that is based on in vivo crosslinking of nucleoside-analog-labeled RNA. The crosslinking positions between RNA and RBP are pin-pointed by characteristic sequence transitions in the cDNA prepared from crosslinked RNA. PAR-CLIP presents a resource for the precise identification of RNP binding sites.

I ♥ *Drosophila*

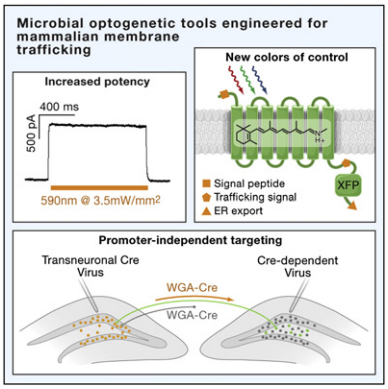
PAGE 142

Heart disease is the most common cause of morbidity and mortality in humans. Using a genome-wide RNAi screen in *Drosophila,* Neely et al. identify 800 candidate genes involved in cardiac development and function. Among them is Not3, part of the CCR4-Not complex implicated in transcriptional regulation. Fly and mouse hearts with reduced Not3 function exhibit poor contraction and heart failure. Humans with NOT3 SNPs also exhibit electrophysiological abnormalities. The findings demonstrate the utility of fly RNAi screens in identifying regulators of mammalian heart function.

Optogenetics Dons Night Goggles

PAGE 154

Optogenetic technologies employ microbial opsins and light pulses to control biological processes within targeted cells in vivo with high temporal precision. Here Gradinaru et al. describe the next generation of optogenetic tools, which enable targeting of cells for optical control solely by virtue of their topological and connectivity relationships within tissue. Furthermore, the authors extend the reach of optogenetic control across the entire visible spectrum up to the infrared border. These results open the door for precise examination of intact neural circuits.



Targeting Placental Growth Factor in Cancer Revisited

PAGE 166 and PAGE 178

Treatment with an anti-placenta growth factor (PlGF) antibody had been previously reported by Carmeliet and colleagues to inhibit angiogenesis and primary tumor growth. Bais et al. now report that PlGF neutralization or genetic ablation of the tyrosine kinase domain of the PlGF receptor, VEGFR-1, did not result in tumor growth inhibition. Their data argue against an important role of PlGF during primary tumor growth and suggest re-evaluation of the clinical potential of anti-PlGF antibodies. Carmeliet and colleagues (Van de Veire et al.) provide new pharmacological and genetic data to further support the merits of targeting PlGF in anticancer therapies.